

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference 110.00810201	FOR FURTHER ACTION See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416)	
International application No. PCT/US99/21581	International filing date (day/month/year) 17/09/1999	Priority date (day/month/year) 17/09/1998
International Patent Classification (IPC) or national classification and IPC G01N33/50		
Applicant REGENTS OF THE UNIVERSITY OF MINNESOTA et al.		

1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.



2. This REPORT consists of a total of 8 sheets, including this cover sheet.

- ☒ This report is also accompanied by ANNEXES, i.e. sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).

These annexes consist of a total of 1 sheets.

3. This report contains indications relating to the following items:

- I ☒ Basis of the report
- II ☒ Priority
- III ☐ Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
- IV ☐ Lack of unity of invention
- V ☒ Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
- VI ☐ Certain documents cited
- VII ☒ Certain defects in the international application
- VIII ☒ Certain observations on the international application

Date of submission of the demand 13/04/2000	Date of completion of this report 23.11.2000
Name and mailing address of the international preliminary examining authority:  European Patent Office D-80298 Munich Tel. +49 89 2399 - 0 Tx: 523656 epmu d Fax: +49 89 2399 - 4465	Authorized officer Stricker, J-E Telephone No. +49 89 2399 8395 

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No. PCT/US99/21581

I. Basis of the report

1. This report has been drawn on the basis of *(substitute sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to the report since they do not contain amendments (Rules 70.16 and 70.17).):*

Description, pages:

1-20,22-30 as originally filed

21 with telefax of 10/04/2000

Claims, No.:

1-49 as originally filed

Drawings, sheets:

1/18-18/18 as originally filed

2. With regard to the **language**, all the elements marked above were available or furnished to this Authority in the language in which the international application was filed, unless otherwise indicated under this item.

These elements were available or furnished to this Authority in the following language: , which is:

- ☐ the language of a translation furnished for the purposes of the international search (under Rule 23.1(b)).
- ☐ the language of publication of the international application (under Rule 48.3(b)).
- ☐ the language of a translation furnished for the purposes of international preliminary examination (under Rule 55.2 and/or 55.3).

3. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international preliminary examination was carried out on the basis of the sequence listing:

- ☐ contained in the international application in written form.
- ☐ filed together with the international application in computer readable form.
- ☐ furnished subsequently to this Authority in written form.
- ☐ furnished subsequently to this Authority in computer readable form.
- ☐ The statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.
- ☐ The statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished.

4. The amendments have resulted in the cancellation of:

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6. Additional observations, if necessary:

II. Priority

- ☐ translation of the earlier application whose priority has been claimed.

2. ☒ This report has been established as if no priority had been claimed due to the fact that the priority claim has been found invalid.

Thus for the purposes of this report, the international filing date indicated above is considered to be the relevant date.

3. Additional observations, if necessary:
see separate sheet

V. Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N) Yes: Claims 1-24, 27-30, 48
No: Claims 25, 26, 31-47, 49

Inventive step (IS) _____ Yes: Claims none
_____ No: Claims 1-49

[illegible]

**2. Citations and explanations
see separate sheet**

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VII. Certain defects in the international application

The following defects in the form or contents of the international application have been noted:
see separate sheet

VIII. Certain observations on the international application

The following observations on the clarity of the claims, description, and drawings or on the question whether the claims are fully supported by the description, are made:
see separate sheet

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EXAMINATION REPORT - SEPARATE SHEET**

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Section II

The priority document does not disclose any device comprising one metabolically active biological material in general (only a few types of cells are mentioned, cf. p.7, 1.8-12) and a non-porous latex-derived material. The priority date is therefore not valid for the subject-matter of the following claims: totally as regards **claims 1-6, 9-32, and 35-49;** partially as regards **claims 7 and 8.**

The document D2 cited in the ISR is thus considered as prior art for the purpose of Art. 33.(2) and (3) PCT as regards the said claims (Rule 64(1) PCT).

Section V

Reference is made to the following documents:

- D1: DATABASE CHEMABS [Online] CHEMICAL ABSTRACTS SERVICE, COLUMBUS, OHIO, US LYNGBERG, OLAV K. ET AL: 'A single use luciferase based biosensor using copolymer-film immobilized viable E. coli HB101.' retrieved from STN XP002127579 & BOOK OF ABSTRACTS, 216TH ACS NATIONAL MEETING, BOSTON, AUGUST 23-27 (1998), BTEC-009 PUBLISHER: AMERICAN CHEMICAL SOCIETY, WASHINGTON, D. C.
- D2: DATABASE CHEMABS [Online] CHEMICAL ABSTRACTS SERVICE, COLUMBUS, OHIO, US LYNGBERG, O. K. ET AL: 'A single-use luciferase-based mercury biosensor using Escherichia coli HB101 immobilized in a latex copolymer film' retrieved from STN Database accession no. 131:268025 XP002127580 & J. IND. MICROBIOL. BIOTECHNOL. (1999), 23(1), 668-676.
- D3: US-A-5 612 184
- D4: WO 90 05910 A
- D5: EP-A-0 318 452

1. D1 discloses a single use mercury biosensor consisting of two porous polymer layers, one of them comprising E. coli cells (cf. abstract). As the porosity usually varies within one polymer, there are at least two portions of different pore size.

- D1 is therefore prejudicial to the novelty of **claims 25, 26, 31-41, 44 and 47** (Art. 33.2) PCT). Since the use of the device is mentioned, the method of **claim 49** is also not novel over D1.
2. D2 discloses a similar device further coated on polyester and specifies some other technical features (cf. abstract). D2 is therefore prejudicial to the novelty of **claims 25, 26, 31, 32, 35-41, 44, 47 and 49** (Art. 33.2) PCT)
 3. Any biological device containing an immobilized active biological material (e.g. those of D1, D2, D4 and D5) is prejudicial to the novelty of the subject-matter of **claims 25 and 26** (as the porosity usually varies within one polymer, there are at least two portions of different pore size).
 4. D3 is cited in the present application on p.2. This document discloses a device for the detection of mercury (cf. columns 3 to 11, in particular c.8 and c.11, l.3) having all the features set out in **claims 31 and 33-47** of the present application. D3 is therefore prejudicial to the novelty of the said claims (Art. 33(2) PCT).
 5. At this stage it should be noted that, even rendered novel, the subject-matter of **claims 32, 42, 43, 45 and 46** would not be considered as inventive since the combination of D1 (or D2) and D3, which would be seriously contemplated by the skilled person, would provide all technical features mentioned in these claims. The reasons therefor are the following: substrates capable of detecting a signal, especially light, are quite known in the art (see e.g. D3, c.8); the biosensor of D3 is capable of detecting a metal in a tissue (cf. c.11, first paragraph); D4 and D5 also disclose the immobilization of the biological material in one or more layers of a polymeric material.
 6. The device of claim 1 differs from those disclosed in D1 and D2 in that it comprises a nonporous latex-derived material. The subject-matter of **claims 1-24**, the method of manufacturing such a device (**claims 27-30**) and the use of the said device (**claim 48**) are therefore novel (Art. 33(2) PCT).

The problem to be solved by the present invention may therefore be regarded as how to create a variety of structures within the device.

The solution proposed in **claim 1** of the present application cannot be considered as involving an inventive step (Article 33(3) PCT) because the feature "nonporous latex-derived material" is merely one of several straightforward possibilities from which the skilled person would select, in accordance with circumstances, without the exercise of inventive skill, in order to solve the problem posed. A similar argumentation applies to the manufacturing and the use of such a device (**claims 27 and 48**).

In view of the cited prior art, dependent **claims 2-24 and 28-30** do not contain any features which, in combination with the features of any claim to which they refer, meet the requirements of the PCT in respect of inventive step.

Section VII

Contrary to the requirements of Rule 5.1(a)(ii) PCT, the relevant background art disclosed in the documents D1, D2, D4 and D5 are not mentioned in the description, nor are these documents identified therein.

Section VIII

1. The term biostructure used in the claims is vague and unclear and leaves the reader in doubt as to the meaning of the technical features to which it refers, thereby rendering the definition of the subject-matter of the concerned claims unclear (Article 6 PCT).
2. Although claims 1, 25 and 31 have been drafted as separate independent claims, they appear to relate effectively to the same subject-matter and to differ from each other only with regard to the definition of the subject-matter for which protection is sought and/or in respect of the terminology used for the features of that subject-matter. The aforementioned claims therefore lack conciseness. Moreover, lack of clarity of the claims as a whole arises, since the plurality of independent claims makes it difficult, if not impossible, to determine the matter for which protection is sought, and places an undue burden on others seeking to establish the extent of

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the protection.

Hence, claims 1, 25 and 31 do not meet the requirements of Article 6 PCT.

The same applies to claims 48 and 49 for similar reasons.

3. The statement which specifies that the non-porous latex-derived material is optional (cf. p.7, l.30-31) is not consistent with claim 1 and renders the latter unclear (Art. 6 PCT).

Figure 10 discloses a device that includes a biostructure in the form of a cell-containing indicator coating coated on a fiber 100, composed of, for example, polyester, nylon, cellulose acetate, or an optical fiber. This fiber can be an optical fiber, for example. As shown in Figure 10A, the coated fiber 100 has an end-stop 101 and a penetrating end 103. The device is shown penetrating through a fish tail. Once a sufficient amount of time has lapsed for the immobilized cells of the cell-containing indicator to be in contact with the fish tissue, the coated fiber 100 is removed. As shown in Figure 10B, the coated fiber 100 is then placed in contact with a photosensitive film 104, which can be in a pouch or container, for example, having nutrients and buffer therein. After a sufficient incubation period, the mercury can be qualitatively detected by viewing a photographic image 105 of the thread on the photosensitive film 104.

Figure 11A shows a cross-section of a coated fiber 100, as shown in Figure 10. The coated fiber 100 includes a monofilament 106 coated with a biostructure 102. The biostructure 102 includes a cell-containing polymeric layer 107 and a polymeric overlayer 108. Figure 11B shows a cross-section of a coated fiber 110 that includes a multiple filament thread 116 with a biostructure 112. The biostructure 112 includes a cell-containing polymeric layer 117 and a polymeric overlayer 118. The coated fiber 110 may also include a polymeric precoat layer 119 between the multiple filament thread 116 and the cell-containing polymeric layer 107.

Figure 12 shows a device 120 in which cells are used that contain a plasmid with a mercury resistance promoter that activates a gene to produce a secreted protease or lipase. The cells are included in a biostructure 122. A pop-up indicator rod 121 is initially held in place by a protein or lipid based glue 123. The pop-up indicator rod 121 may be used either qualitatively or quantitatively, if it includes an indicator scale (not shown). The device also includes a spring 125 under tension that is attached to the pop-up indicator rod 121. In use, the device 120 is inserted into fish tissue. When mercury is detected by the cells in the biostructure 122 as it diffuses through a perforated housing 126 of device 120, the resulting protease or lipase degrades the glue 122 and releases the rod 121. As a result of the tension placed on the rod 121 by the spring 125, the rod moves up. By the design of the rod, the glue, and the glue holder the device could be made to be quantitative. Alternately, the pop-up indicator rod 121

PCT

INTERNATIONAL SEARCH REPORT

(PCT Article 18 and Rules 43 and 44)

Applicant's or agent's file reference 110.00810201	FOR FURTHER ACTION see Notification of Transmittal of International Search Report (Form PCT/ISA/220) as well as, where applicable, item 5 below.	
International application No. PCT/US 99/ 21581	International filing date (day/month/year) 17/09/1999	(Earliest) Priority Date (day/month/year) 17/09/1998
Applicant REGENTS OF THE UNIVERSITY OF MINNESOTA et al.		

This International Search Report has been prepared by this International Searching Authority and is transmitted to the applicant according to Article 18. A copy is being transmitted to the International Bureau.

This International Search Report consists of a total of 3 sheets.

☒ It is also accompanied by a copy of each prior art document cited in this report.

1. Basis of the report

a. With regard to the **language**, the international search was carried out on the basis of the international application in the language in which it was filed, unless otherwise indicated under this item.

☐ the international search was carried out on the basis of a translation of the international application furnished to this Authority (Rule 23.1(b)).

b. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international search was carried out on the basis of the sequence listing :

☐ contained in the international application in written form.

☐ filed together with the international application in computer readable form.

☐ furnished subsequently to this Authority in written form.

☐ furnished subsequently to this Authority in computer readable form.

☐ the statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.

☐ the statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished

2. ☐ **Certain claims were found unsearchable** (See Box I).

3. ☐ **Unity of invention is lacking** (see Box II).

4. With regard to the **title**,

☒ the text is approved as submitted by the applicant.

☐ the text has been established by this Authority to read as follows:

5. With regard to the **abstract**,

☒ the text is approved as submitted by the applicant.

☐ the text has been established, according to Rule 38.2(b), by this Authority as it appears in Box III. The applicant may, within one month from the date of mailing of this international search report, submit comments to this Authority.

6. The figure of the **drawings** to be published with the abstract is Figure No.

☒ as suggested by the applicant.

☐ because the applicant failed to suggest a figure.

☐ because this figure better characterizes the invention.

1
☐ None of the figures.

INTERNATIONAL SEARCH REPORT

International Application No

US 99/21581

A. CLASSIFICATION OF SUBJECT MATTER

IPC 7 G01N33/50 C12Q1/02 C12Q1/66

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 7 G01N C12Q

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	<p>DATABASE CHEMABS 'Online! CHEMICAL ABSTRACTS SERVICE, COLUMBUS, OHIO, US LYNGBERG, OLAV K. ET AL: "A single use luciferase based biosensor using copolymer-film immobilized viable E. coli HB101." retrieved from STN XP002127579 abstract & BOOK OF ABSTRACTS, 216TH ACS NATIONAL MEETING, BOSTON, AUGUST 23-27 (1998), BTEC-009 PUBLISHER: AMERICAN CHEMICAL SOCIETY, WASHINGTON, D. C. , --- -/--</p>	1-49



Further documents are listed in the continuation of box C.



Patent family members are listed in annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search

14 January 2000

Date of mailing of the international search report

27/01/2000

Name and mailing address of the ISA

European Patent Office, P.B. 5818 Patentlaan 2
 NL - 2280 HV Rijswijk
 Tel. (+31-70) 340-2040, Tx. 31 651 epo nl,
 Fax: (+31-70) 340-3016

Authorized officer

Moreno, C

INTERNATIONAL SEARCH REPORT

International Application No

P US 99/21581

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
P,X	<p>DATABASE CHEMABS 'Online! CHEMICAL ABSTRACTS SERVICE, COLUMBUS, OHIO, US LYNGBERG, O. K. ET AL: "A single-use luciferase-based mercury biosensor using Escherichia coli HB101 immobilized in a latex copolymer film" retrieved from STN Database accession no. 131:268025 XP002127580 abstract & J. IND. MICROBIOL. BIOTECHNOL. (1999), 23(1), 668-676 ,</p>	1-49
A	<p>PATENT ABSTRACTS OF JAPAN vol. 011, no. 369 (C-461), 2 December 1987 (1987-12-02) & JP 62 138502 A (TOKUYAMA SODA CO LTD), 22 June 1987 (1987-06-22) abstract</p>	1,25-27, 31
A	<p>US 5 612 184 A (ROSSON REINHARDT A) 18 March 1997 (1997-03-18) cited in the application the whole document</p>	1,25-27, 31
A	<p>WO 90 05910 A (I STAT CORP) 31 May 1990 (1990-05-31) the whole document</p>	1,25-27, 31
A	<p>EP 0 318 452 A (MONSANTO EUROPE SA) 31 May 1989 (1989-05-31) abstract</p>	1,25-27, 31
A	<p>PATENT ABSTRACTS OF JAPAN vol. 012, no. 186 (C-500), 31 May 1988 (1988-05-31) & JP 62 294083 A (MITSUBISHI RAYON CO LTD;OTHERS: 01), 21 December 1987 (1987-12-21) abstract</p>	1,25-27, 31

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

US 99/21581

Patent document cited in search report		Publication date	Patent family member(s)	Publication date
JP 62138502	A	22-06-1987	JP 8026092 B	13-03-1996
US 5612184	A	18-03-1997	US 5571722 A	05-11-1996
			AU 2422792 A	02-03-1993
			CA 2114103 A	18-02-1993
			EP 0597984 A	25-05-1994
			JP 6509712 T	02-11-1994
			WO 9303179 A	18-02-1996
WO 9005910	A	31-05-1990	CA 2002848 A	14-05-1990
			CA 2221178 A	14-05-1990
			EP 0442969 A	28-08-1991
			JP 4503249 T	11-06-1992
			SG 45431 A	16-01-1998
			US 5554339 A	10-09-1996
			US 5200051 A	06-04-1993
			US 5837446 A	17-11-1998
			US 5837454 A	17-11-1998
			US 5063081 A	05-11-1991
			US 5212050 A	18-05-1993
			US 5466575 A	14-11-1995
EP 0318452	A	31-05-1989	AT 90383 T	15-06-1993
			CA 1296060 A	18-02-1992
			DE 3881653 A	15-07-1993
			DE 3881653 T	20-01-1994
			DK 600388 A	30-04-1989
			ES 2058339 T	01-11-1994
			US 4983510 A	08-01-1991
JP 62294083	A	21-12-1987	NONE	

PATENT COOPERATION TREATY

D✓

From the INTERNATIONAL SEARCHING AUTHORITY

PCT

NOTIFICATION OF TRANSMITTAL OF
THE INTERNATIONAL SEARCH REPORT
OR THE DECLARATION

(PCT Rule 44.1)

To:
MUETING, Ann M.
MUETING, RAASCH & GEBHARDT, P.A.
P.O. Box 581415
Minneapolis, MN 55458-1415
UNITED STATES OF AMERICA

Date of mailing
(day/month/year) **27/01/2000**

Applicant's or agent's file reference
110.00810201

FOR FURTHER ACTION See paragraphs 1 and 4 below

International application No.
PCT/US 99/21581

International filing date
(day/month/year) **17/09/1999**

Applicant

REGENTS OF THE UNIVERSITY OF MINNESOTA et al.

1. ☒ The applicant is hereby notified that the International Search Report has been established and is transmitted herewith.

Filing of amendments and statement under Article 19:

The applicant is entitled, if he so wishes, to amend the claims of the International Application (see Rule 46):

When? The time limit for filing such amendments is normally 2 months from the date of transmittal of the International Search Report; however, for more details, see the notes on the accompanying sheet.

Where? Directly to the International Bureau of WIPO
34, chemin des Colombettes
1211 Geneva 20, Switzerland
Facsimile No.: (41-22) 740.14.35

For more detailed instructions, see the notes on the accompanying sheet.

2. ☐ The applicant is hereby notified that no International Search Report will be established and that the declaration under Article 17(2)(a) to that effect is transmitted herewith.

3. ☐ **With regard to the protest** against payment of (an) additional fee(s) under Rule 40.2, the applicant is notified that:

☐ the protest together with the decision thereon has been transmitted to the International Bureau together with the applicant's request to forward the texts of both the protest and the decision thereon to the designated Offices.


☐ no decision has been made yet on the protest; the applicant will be notified as soon as a decision is made.

4. **Further action(s):** The applicant is reminded of the following:

Shortly after **18 months** from the priority date, the international application will be published by the International Bureau. If the applicant wishes to avoid or postpone publication, a notice of withdrawal of the international application, or of the priority claim, must reach the International Bureau as provided in Rules 90bis.1 and 90bis.3, respectively, before the completion of the technical preparations for international publication.

Within **19 months** from the priority date, a demand for international preliminary examination must be filed if the applicant wishes to postpone the entry into the national phase until 30 months from the priority date (in some Offices even later).

Within **20 months** from the priority date, the applicant must perform the prescribed acts for entry into the national phase before all designated Offices which have not been elected in the demand or in a later election within 19 months from the priority date or could not be elected because they are not bound by Chapter II.

Name and mailing address of the International Searching Authority
 European Patent Office, P.B. 5818 Patentlaan 2
NL-2280 HV Rijswijk
Tel. (+31-70) 340-2040, Tx. 31 651 epo nl.
Fax: (+31-70) 340-3016

Authorized officer

Jaap Hurenkamp

RECEIVED

FEB 03 2000

MUETING AND RAASCH

These Notes are intended to give the basic instructions concerning the filing of amendments under article 19. The Notes are based on the requirements of the Patent Cooperation Treaty, the Regulations and the Administrative Instructions under that Treaty. In case of discrepancy between these Notes and those requirements, the latter are applicable. For more detailed information, see also the PCT Applicant's Guide, a publication of WIPO.

In these Notes, "Article", "Rule", and "Section" refer to the provisions of the PCT, the PCT Regulations and the PCT Administrative Instructions respectively.

INSTRUCTIONS CONCERNING AMENDMENTS UNDER ARTICLE 19

The applicant has, after having received the international search report, one opportunity to amend the claims of the international application. It should however be emphasized that, since all parts of the international application (claims, description and drawings) may be amended during the international preliminary examination procedure, there is usually no need to file amendments of the claims under Article 19 except where, e.g. the applicant wants the latter to be published for the purposes of provisional protection or has another reason for amending the claims before international publication. Furthermore, it should be emphasized that provisional protection is available in some States only.

What parts of the international application may be amended?

Under Article 19, only the claims may be amended.

During the international phase, the claims may also be amended (or further amended) under Article 34 before the International Preliminary Examining Authority. The description and drawings may only be amended under Article 34 before the International Examining Authority.

Upon entry into the national phase, all parts of the international application may be amended under Article 28 or, where applicable, Article 41.

When?

Within 2 months from the date of transmittal of the international search report or 16 months from the priority date, whichever time limit expires later. It should be noted, however, that the amendments will be considered as having been received on time if they are received by the International Bureau after the expiration of the applicable time limit but before the completion of the technical preparations for international publication (Rule 46.1).

Where not to file the amendments?

The amendments may only be filed with the International Bureau and not with the receiving Office or the International Searching Authority (Rule 46.2).

Where a demand for international preliminary examination has been/is filed, see below.

How?

Either by cancelling one or more entire claims, by adding one or more new claims or by amending the text of one or more of the claims as filed.

A replacement sheet must be submitted for each sheet of the claims which, on account of an amendment or amendments, differs from the sheet originally filed.

All the claims appearing on a replacement sheet must be numbered in Arabic numerals. Where a claim is cancelled, no renumbering of the other claims is required. In all cases where claims are renumbered, they must be renumbered consecutively (Administrative Instructions, Section 205(b)).

The amendments must be made in the language in which the international application is to be published.

What documents must/may accompany the amendments?

Letter (Section 205(b)):

The amendments must be submitted with a letter.

The letter will not be published with the international application and the amended claims. It should not be confused with the "Statement under Article 19(1)" (see below, under "Statement under Article 19(1)").

The letter must be in English or French, at the choice of the applicant. However, if the language of the international application is English, the letter must be in English; if the language of the international application is French, the letter must be in French.

The letter must indicate the differences between the claims as filed and the claims as amended. It must, in particular, indicate, in connection with each claim appearing in the international application (it being understood that identical indications concerning several claims may be grouped), whether

- (i) the claim is unchanged;
- (ii) the claim is cancelled;
- (iii) the claim is new;
- (iv) the claim replaces one or more claims as filed;
- (v) the claim is the result of the division of a claim as filed.

The following examples illustrate the manner in which amendments must be explained in the accompanying letter:

1. [Where originally there were 48 claims and after amendment of some claims there are 51]:
"Claims 1 to 29, 31, 32, 34, 35, 37 to 48 replaced by amended claims bearing the same numbers; claims 30, 33 and 36 unchanged; new claims 49 to 51 added."
2. [Where originally there were 15 claims and after amendment of all claims there are 11]:
"Claims 1 to 15 replaced by amended claims 1 to 11."
3. [Where originally there were 14 claims and the amendments consist in cancelling some claims and in adding new claims]:
"Claims 1 to 6 and 14 unchanged; claims 7 to 13 cancelled; new claims 15, 16 and 17 added." or
"Claims 7 to 13 cancelled; new claims 15, 16 and 17 added; all other claims unchanged."
4. [Where various kinds of amendments are made]:
"Claims 1-10 unchanged; claims 11 to 13, 18 and 19 cancelled; claims 14, 15 and 16 replaced by amended claim 14; claim 17 subdivided into amended claims 15, 16 and 17; new claims 20 and 21 added."

"Statement under article 19(1)" (Rule 46.4)

The amendments may be accompanied by a statement explaining the amendments and indicating any impact that such amendments might have on the description and the drawings (which cannot be amended under Article 19(1)).

The statement will be published with the international application and the amended claims.

It must be in the language in which the international application is to be published.

It must be brief, not exceeding 500 words if in English or if translated into English.

It should not be confused with and does not replace the letter indicating the differences between the claims as filed and as amended. It must be filed on a separate sheet and must be identified as such by a heading, preferably by using the words "Statement under Article 19(1)."

It may not contain any disparaging comments on the international search report or the relevance of citations contained in that report. Reference to citations, relevant to a given claim, contained in the international search report may be made only in connection with an amendment of that claim.

Consequence if a demand for international preliminary examination has already been filed

If, at the time of filing any amendments under Article 19, a demand for international preliminary examination has already been submitted, the applicant must preferably, at the same time of filing the amendments with the International Bureau, also file a copy of such amendments with the International Preliminary Examining Authority (see Rule 62.2(a), first sentence).

Consequence with regard to translation of the international application for entry into the national phase

The applicant's attention is drawn to the fact that, where upon entry into the national phase, a translation of the claims as amended under Article 19 may have to be furnished to the designated/elected Offices, instead of, or in addition to, the translation of the claims as filed.

For further details on the requirements of each designated/elected Office, see Volume II of the PCT Applicant's Guide.

PATENT COOPERATION TREATY

DV

From the INTERNATIONAL BUREAU

PCT

NOTICE INFORMING THE APPLICANT OF THE COMMUNICATION OF THE INTERNATIONAL APPLICATION TO THE DESIGNATED OFFICES

(PCT Rule 47.1(c), first sentence)

To:

MUETING, Ann, M.
Mueting, Raasch & Gebhardt, P.A.
P.O. Box 581415
Minneapolis, MN 55458-1415
ETATS-UNIS D'AMERIQUE

Date of mailing (day/month/year)

23 March 2000 (23.03.00)

Applicant's or agent's file reference

110.00810201

IMPORTANT NOTICE

International application No.

PCT/US99/21581

International filing date (day/month/year)

17 September 1999 (17.09.99)

Priority date (day/month/year)

17 September 1998 (17.09.98)

Applicant

REGENTS OF THE UNIVERSITY OF MINNESOTA et al

1. Notice is hereby given that the International Bureau has communicated, as provided in Article 20, the international application to the following designated Offices on the date indicated above as the date of mailing of this Notice:

AU,CN,JP,KP,KR,US

In accordance with Rule 47.1(c), third sentence, those Offices will accept the present Notice as conclusive evidence that the communication of the international application has duly taken place on the date of mailing indicated above and no copy of the international application is required to be furnished by the applicant to the designated Office(s).

2. The following designated Offices have waived the requirement for such a communication at this time:

AE,AL,AM,AP,AT,AZ,BA,BB,BG,BR,BY,CA,CH,CR,CU,CZ,DE,DK,DM,EA,EE,EP,ES,FI,GB,GD,GE,
GH,GM,HR,HU,ID,IL,IN,IS,KE,KG,KZ,LC,LK,LR,LS,LT,LU,LV,MD,MG,MK,MN,MW,MX,NO,NZ,OA,
PL,PT,RO,RU,SD,SE,SG,SI,SK,SL,TJ,TM,TR,TT,UA,UG,UZ,VN,YU,ZA,ZW

The communication will be made to those Offices only upon their request. Furthermore, those Offices do not require the applicant to furnish a copy of the international application (Rule 49.1(a-bis)).

3. Enclosed with this Notice is a copy of the international application as published by the International Bureau on

23 March 2000 (23.03.00) under No. WO 00/16098

REMINDER REGARDING CHAPTER II (Article 31(2)(a) and Rule 54.2)

If the applicant wishes to postpone entry into the national phase until 30 months (or later in some Offices) from the priority date, a **demand for international preliminary examination** must be filed with the competent International Preliminary Examining Authority before the expiration of 19 months from the priority date.

It is the applicant's sole responsibility to monitor the 19-month time limit.

Note that only an applicant who is a national or resident of a PCT Contracting State which is bound by Chapter II has the right to file a demand for international preliminary examination.

REMINDER REGARDING ENTRY INTO THE NATIONAL PHASE (Article 22 or 39(1))

If the applicant wishes to proceed with the international application in the **national phase**, he must, within 20 months or 30 months, or later in some Offices, perform the acts referred to therein before each designated or elected Office.

For further important information on the time limits and acts to be performed for entering the national phase, see the Annex to Form PCT/IB/301 (Notification of Receipt of Record Copy) and Volume II of the PCT Applicant's Guide.

RECEIVED

APR 06 2000

The International Bureau of WIPO
34, chemin des Colombettes
1211 Geneva 20, Switzerland

Facsimile No. (41-22) 740.14.35

Authorized officer

J. Zahra **MUETING AND RAASCH**

Telephone No. (41-22) 338.83.38



REQUEST

The undersigned requests that the present international application be processed according to the Patent Cooperation Treaty.

For Receiving Office use only

International Application No.

International Filing Date

Name of receiving Office and "PCT International Application"

Applicant's or agent's file reference
(if desired) (12 characters maximum) 110.00810201

Box No. I TITLE OF INVENTION

COMPOSITE DEVICES INCORPORATING BIOLOGICAL MATERIAL AND METHODS

Box No. II APPLICANT

Name and address: (Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country. The country of the address indicated in this Box is the applicant's State (that is, country) of residence if no State of residence is indicated below.)

REGENTS OF THE UNIVERSITY OF MINNESOTA
100 Church Street Southeast
Minneapolis, Minnesota 55455
United States of America

☐ This person is also inventor.

Telephone No.

Facsimile No.

Teleprinter No.

State (that is, country) of nationality:
US

State (that is, country) of residence:
US

This person is applicant for the purposes of: ☐ all designated States ☒ all designated States except the United States of America ☐ the United States of America only ☐ the States indicated in the Supplemental Box

Box No. III FURTHER APPLICANT(S) AND/OR (FURTHER) INVENTOR(S)

Name and address: (Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country. The country of the address indicated in this Box is the applicant's State (that is, country) of residence if no State of residence is indicated below.)

LYNGBERG, Olav K.
1022 Marvel Street
Apartment 10
St. Paul, Minnesota 55114
United States of America

This person is:

☐ applicant only

☒ applicant and inventor

☐ inventor only (If this check-box is marked, do not fill in below.)

State (that is, country) of nationality:
US

State (that is, country) of residence:
US

This person is applicant for the purposes of: ☐ all designated States ☐ all designated States except the United States of America ☒ the United States of America only ☐ the States indicated in the Supplemental Box

☒ Further applicants and/or (further) inventors are indicated on a continuation sheet.

Box No. IV AGENT OR COMMON REPRESENTATIVE; OR ADDRESS FOR CORRESPONDENCE

The person identified below is hereby/has been appointed to act on behalf of the applicant(s) before the competent International Authorities as:

☒ agent ☐ common representative

Name and address: (Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country.)

MUETING, Ann M.
MUETING, RAASCH & GEBHARDT, P.A.
P.O. Box 581415
Minneapolis, Minnesota 55458-1415
United States of America

Telephone No.
(612)305-1217

Facsimile No.
(612)305-1228

Teleprinter No.

☐ Address for correspondence: Mark this check-box where no agent or common representative is/has been appointed and the space above is used instead to indicate a special address to which correspondence should be sent.

Continuation of Box No. III FURTHER APPLICANTS AND/OR (FURTHER) INVENTOR(S)

If none of the following sub-boxes is used, this sheet is not to be included in the request.

Name and address: (Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country. The country of the address indicated in this Box is the applicant's State (that is, country) of residence if no State of residence is indicated below.)

FLICKINGER, Michael C.
2226 Scudder Avenue
St. Paul, Minnesota 55108
United States of America

This person is:

- ☐ applicant only
☒ applicant and inventor
☐ inventor only (If this check-box is marked, do not fill in below.)

State (that is, country) of nationality:
US

State (that is, country) of residence:
US

This person is applicant for the purposes of: ☐ all designated States ☐ all designated States except the United States of America ☒ the United States of America only ☐ the States indicated in the Supplemental Box

Name and address: (Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country. The country of the address indicated in this Box is the applicant's State (that is, country) of residence if no State of residence is indicated below.)

SCRIVEN, L. E. (Edward) II
2044 Cedar Lake Parkway
Minneapolis, Minnesota 55416
United States of America

This person is:

- ☐ applicant only
☒ applicant and inventor
☐ inventor only (If this check-box is marked, do not fill in below.)

State (that is, country) of nationality:
US

State (that is, country) of residence:
US

This person is applicant for the purposes of: ☐ all designated States ☐ all designated States except the United States of America ☒ the United States of America only ☐ the States indicated in the Supplemental Box

Name and address: (Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country. The country of the address indicated in this Box is the applicant's State (that is, country) of residence if no State of residence is indicated below.)

ANDERSON, Ron
13645 Garrett Avenue
Apple Valley, Minnesota 55124
United States of America

This person is:

- ☐ applicant only
☒ applicant and inventor
☐ inventor only (If this check-box is marked, do not fill in below.)

State (that is, country) of nationality:
US

State (that is, country) of residence:
US

This person is applicant for the purposes of: ☐ all designated States ☐ all designated States except the United States of America ☒ the United States of America only ☐ the States indicated in the Supplemental Box

Name and address: (Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country. The country of the address indicated in this Box is the applicant's State (that is, country) of residence if no State of residence is indicated below.)

This person is:

- ☐ applicant only
☐ applicant and inventor
☐ inventor only (If this check-box is marked, do not fill in below.)

State (that is, country) of nationality:

State (that is, country) of residence:

This person is applicant for the purposes of: ☐ all designated States ☐ all designated States except the United States of America ☐ the United States of America only ☐ the States indicated in the Supplemental Box

☐ Further applicants and/or (further) inventors are indicated on another continuation sheet.

Box No.V DESIGNATION OF STATES

The following designations are hereby made under Rule 4.9(a) (mark the applicable check-boxes; at least one must be marked):

Regional Patent

- ☒ **AP ARIPO Patent:** GH Ghana, GM Gambia, KE Kenya, LS Lesotho, MW Malawi, SD Sudan, SL Sierra Leone, SZ Swaziland, UG Uganda, ZW Zimbabwe, and any other State which is a Contracting State of the Harare Protocol and of the PCT
- ☒ **EA Eurasian Patent:** AM Armenia, AZ Azerbaijan, BY Belarus, KG Kyrgyzstan, KZ Kazakhstan, MD Republic of Moldova, RU Russian Federation, TJ Tajikistan, TM Turkmenistan, and any other State which is a Contracting State of the Eurasian Patent Convention and of the PCT
- ☒ **EP European Patent:** AT Austria, BE Belgium, CH and LI Switzerland and Liechtenstein, CY Cyprus, DE Germany, DK Denmark, ES Spain, FI Finland, FR France, GB United Kingdom, GR Greece, IE Ireland, IT Italy, LU Luxembourg, MC Monaco, NL Netherlands, PT Portugal, SE Sweden, and any other State which is a Contracting State of the European Patent Convention and of the PCT
- ☒ **OA OAPI Patent:** BF Burkina Faso, BJ Benin, CF Central African Republic, CG Congo, CI Côte d'Ivoire, CM Cameroon, GA Gabon, GN Guinea, GW Guinea-Bissau, ML Mali, MR Mauritania, NE Niger, SN Senegal, TD Chad, TG Togo, and any other State which is a member State of OAPI and a Contracting State of the PCT (if other kind of protection or treatment desired, specify on dotted line)

National Patent (if other kind of protection or treatment desired, specify on dotted line):

- | | |
|---|--|
| <input checked="" type="checkbox"/> AE United Arab Emirates | <input checked="" type="checkbox"/> LR Liberia |
| <input checked="" type="checkbox"/> AL Albania | <input checked="" type="checkbox"/> LS Lesotho |
| <input checked="" type="checkbox"/> AM Armenia | <input checked="" type="checkbox"/> LT Lithuania |
| <input checked="" type="checkbox"/> AT Austria | <input checked="" type="checkbox"/> LU Luxembourg |
| <input checked="" type="checkbox"/> AU Australia | <input checked="" type="checkbox"/> LV Latvia |
| <input checked="" type="checkbox"/> AZ Azerbaijan | <input checked="" type="checkbox"/> MD Republic of Moldova |
| <input checked="" type="checkbox"/> BA Bosnia and Herzegovina | <input checked="" type="checkbox"/> MG Madagascar |
| <input checked="" type="checkbox"/> BB Barbados | <input checked="" type="checkbox"/> MK The former Yugoslav Republic of Macedonia |
| <input checked="" type="checkbox"/> BG Bulgaria | |
| <input checked="" type="checkbox"/> BR Brazil | <input checked="" type="checkbox"/> MN Mongolia |
| <input checked="" type="checkbox"/> BY Belarus | <input checked="" type="checkbox"/> MW Malawi |
| <input checked="" type="checkbox"/> CA Canada | <input checked="" type="checkbox"/> MX Mexico |
| <input checked="" type="checkbox"/> CH and LI Switzerland and Liechtenstein | <input checked="" type="checkbox"/> NO Norway |
| <input checked="" type="checkbox"/> CN China | <input checked="" type="checkbox"/> NZ New Zealand |
| <input checked="" type="checkbox"/> CU Cuba | <input checked="" type="checkbox"/> PL Poland |
| <input checked="" type="checkbox"/> CZ Czech Republic | <input checked="" type="checkbox"/> PT Portugal |
| <input checked="" type="checkbox"/> DE Germany | <input checked="" type="checkbox"/> RO Romania |
| <input checked="" type="checkbox"/> DK Denmark | <input checked="" type="checkbox"/> RU Russian Federation |
| <input checked="" type="checkbox"/> EE Estonia | <input checked="" type="checkbox"/> SD Sudan |
| <input checked="" type="checkbox"/> ES Spain | <input checked="" type="checkbox"/> SE Sweden |
| <input checked="" type="checkbox"/> FI Finland | <input checked="" type="checkbox"/> SG Singapore |
| <input checked="" type="checkbox"/> GB United Kingdom | <input checked="" type="checkbox"/> SI Slovenia |
| <input checked="" type="checkbox"/> GD Grenada | <input checked="" type="checkbox"/> SK Slovakia |
| <input checked="" type="checkbox"/> GE Georgia | <input checked="" type="checkbox"/> SL Sierra Leone |
| <input checked="" type="checkbox"/> GH Ghana | <input checked="" type="checkbox"/> TJ Tajikistan |
| <input checked="" type="checkbox"/> GM Gambia | <input checked="" type="checkbox"/> TM Turkmenistan |
| <input checked="" type="checkbox"/> HR Croatia | <input checked="" type="checkbox"/> TR Turkey |
| <input checked="" type="checkbox"/> HU Hungary | <input checked="" type="checkbox"/> TT Trinidad and Tobago |
| <input checked="" type="checkbox"/> ID Indonesia | <input checked="" type="checkbox"/> UA Ukraine |
| <input checked="" type="checkbox"/> IL Israel | <input checked="" type="checkbox"/> UG Uganda |
| <input checked="" type="checkbox"/> IN India | <input checked="" type="checkbox"/> US United States of America |
| <input checked="" type="checkbox"/> IS Iceland | |
| <input checked="" type="checkbox"/> JP Japan | <input checked="" type="checkbox"/> UZ Uzbekistan |
| <input checked="" type="checkbox"/> KE Kenya | <input checked="" type="checkbox"/> VN Viet Nam |
| <input checked="" type="checkbox"/> KG Kyrgyzstan | <input checked="" type="checkbox"/> YU Yugoslavia |
| <input checked="" type="checkbox"/> KP Democratic People's Republic of Korea | <input checked="" type="checkbox"/> ZA South Africa |
| | <input checked="" type="checkbox"/> ZW Zimbabwe |
| <input checked="" type="checkbox"/> KR Republic of Korea | Check-boxes reserved for designating States which have become party to the PCT after issuance of this sheet: |
| <input checked="" type="checkbox"/> KZ Kazakhstan | <input checked="" type="checkbox"/> CR Costa Rica |
| <input checked="" type="checkbox"/> LC Saint Lucia | <input checked="" type="checkbox"/> DM Dominica |
| <input checked="" type="checkbox"/> LK Sri Lanka | |

Precautionary Designation Statement: In addition to the designations made above, the applicant also makes under Rule 4.9(b) all other designations which would be permitted under the PCT except any designation(s) indicated in the Supplemental Box as being excluded from the scope of this statement. The applicant declares that those additional designations are subject to confirmation and that any designation which is not confirmed before the expiration of 15 months from the priority date is to be regarded as withdrawn by the applicant at the expiration of that time limit. (Confirmation of a designation consists of the filing of a notice specifying that designation and the payment of the designation and confirmation fees. Confirmation must reach the receiving Office within the 15-month time limit.)

Box No. VI PRIORITY CLAIM					<input type="checkbox"/> Further priority claim indicated in the Supplemental Box.	
Filing date of earlier application (day/month/year)	Number of earlier application	Where earlier application is:				
		national application: country	regional application:* regional Office	international application: receiving Office		
item (1) 17 September 1998 (17.09.98)	60/100,914	US				
item (2)						
item (3)						
<input checked="" type="checkbox"/> The receiving Office is requested to prepare and transmit to the International Bureau a certified copy of the earlier application(s) (only if the earlier application was filed with the Office which for the purposes of the present international application is the receiving Office) identified above as item(s): <u>(1)</u> <small>* Where the earlier application is an ARIPO application, it is mandatory to indicate in the Supplemental Box at least one country party to the Paris Convention for the Protection of Industrial Property for which that earlier application was filed (Rule 4.10(b)(ii)). See Supplemental Box.</small>						
Box No. VII INTERNATIONAL SEARCHING AUTHORITY						
Choice of International Searching Authority (ISA) (if two or more International Searching Authorities are competent to carry out the international search, indicate the Authority chosen; the two-letter code may be used): ISA/EP			Request to use results of earlier search; reference to that search (if an earlier search has been carried out by or requested from the International Searching Authority): Date (day/month/year) Number Country (or regional Office)			
Box No. VIII CHECK LIST: LANGUAGE OF FILING						
This international application contains the following number of sheets: request : 4 description (excluding sequence listing part) : 30 claims : 4 abstract : 1 drawings : 18 sequence listing part of description : 0 Total number of sheets : 57		This international application is accompanied by the item(s) marked below: 1. <input checked="" type="checkbox"/> fee calculation sheet 2. <input type="checkbox"/> separate signed power of attorney 3. <input checked="" type="checkbox"/> copy of general power of attorney; reference number, if any: 4. <input type="checkbox"/> statement explaining lack of signature 5. <input type="checkbox"/> priority document(s) identified in Box No. VI as item(s): 6. <input type="checkbox"/> translation of international application into (language): 7. <input type="checkbox"/> separate indications concerning deposited microorganism or other biological material 8. <input type="checkbox"/> nucleotide and/or amino acid sequence listing in computer readable form 9. <input checked="" type="checkbox"/> other (specify): Itemized return-stamped postcard, Transmittal Letter				
Figure of the drawings which should accompany the abstract: 1		Language of filing of the international application: English				
Box No. IX SIGNATURE OF APPLICANT OR AGENT						
Next to each signature, indicate the name of the person signing and the capacity in which the person signs (if such capacity is not obvious from reading the request). <div style="display: flex; align-items: center; margin-top: 20px;"> <div style="margin-right: 20px;">SANDBERG, Victoria A.</div> </div>						

For receiving Office use only		2. Drawings: <input type="checkbox"/> received: <input type="checkbox"/> not received:
1. Date of actual receipt of the purported international application:		
3. Corrected date of actual receipt due to later but timely received papers or drawings completing the purported international application:		
4. Date of timely receipt of the required corrections under PCT Article 11(2):		
5. International Searching Authority (if two or more are competent): ISA/		6. <input type="checkbox"/> Transmittal of search copy delayed until search fee is paid

For International Bureau use only	
Date of receipt of the record copy by the International Bureau:	